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new claims are identical to the previously submitted versions thereof. No claims have been added or canceled. Accordingly, claims 1-137 are still pending.

In new claims 1, 29 and 49, the language "polypeptide capable of binding with a $p75^{NTR}$ receptor" has been replaced with the language "$p75^{NTR}$-associated cell death executor" in order to more clearly set forth that which applicant claims as the invention. Support for the language can be found in the specification at, *inter alia*, page 1, lines 29-31. Therefore, applicant submits that the addition of new claims 1, 29 and 49 raises no issue of new matter.

Formalities

In item III of the Written Opinion, the Examiner stated that claims 5-7, 12, 15, 26-28, 32, 33, 35-37, 39-48 and 50-137 will not be examined with regard to novelty, inventive step or industrial applicability. Applicant notes, however, that claim 5 has in fact been examined with respect to novelty.

Applicant acknowledges the Examiner's statement in item V that claims 1-5, 8-11, 13, 14, 16-25, 29-31, 34, 35, 38 and 49 meet the criteria set out in PCT Article 33(4) because the nucleic acid sequence, vector encoding the sequence, host cell containing the vector and the purified polypeptide made by the host cell are useful in studying ligand-$p75^{NTR}$ receptor interactions.

Objection Under PCT Article 33(2)

The Examiner objected to claims 1-5, 8-11, 13, 14, 16-25, 29-31, 34, 35, 38 and 49 under PCT Article 33(2) as allegedly lacking novelty over Iwane, et al.

In response to the Examiner's objection, but without conceding the correctness thereof, applicant has added new claims 1, 29 and 49 which relate to a $p75^{NTR}$-associated cell death executor as opposed

to a polypeptide capable of binding to a $p75^{NTR}$ receptor. Applicant maintains that the claims, as amended, overcome the Examiner's objection.

The Examiner also objected to claims 1-5, 8-11, 13, 14, 16-25, 29-31, 34, 35, 38 and 49 under PCT Article 33(2) as allegedly lacking novelty over Khursigara, et al. For the reasons set forth above, applicant maintains that the claims, as amended, overcome this rejection.

In view of the above remarks, claims 1-5, 8-11, 13, 14, 16-25, 29-31, 34, 35, 38 and 49 satisfy the requirements of PCT Article 33(2).

PCT Article 5 and PCT Rules 5.1(a) and 66.2(a)(v)

In item VIII, the Examiner objected to claims 1-5, 8-11, 13, 14, 16-25, 29-31, 34, 35, 38 and 49 as allegedly lacking clarity under PCT Rule 66.2(a)(v), since practice of the invention is not adequately described or enabled as required under PCT Rule 5.1(a). Similarly, the Examiner objected to the description under PCT Rule 66.2(a)(v) as allegedly lacking clarity under PCT Article 5, since it fails to adequately describe or enable the claimed invention.

In response, but without conceding the correctness of the Examiner's objections, applicant maintains that the claims as amended overcome these objections for the reasons discussed above.

In view of the above remarks, applicant maintains that claims 1-5, 8-11, 13, 14, 16-25, 29-31, 34, 35, 38 and 49 and the description satisfy the requirements of PCT Article 5, and PCT Rules 5.1(a) and 66.2(a)(v).

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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Registration No. 37,399
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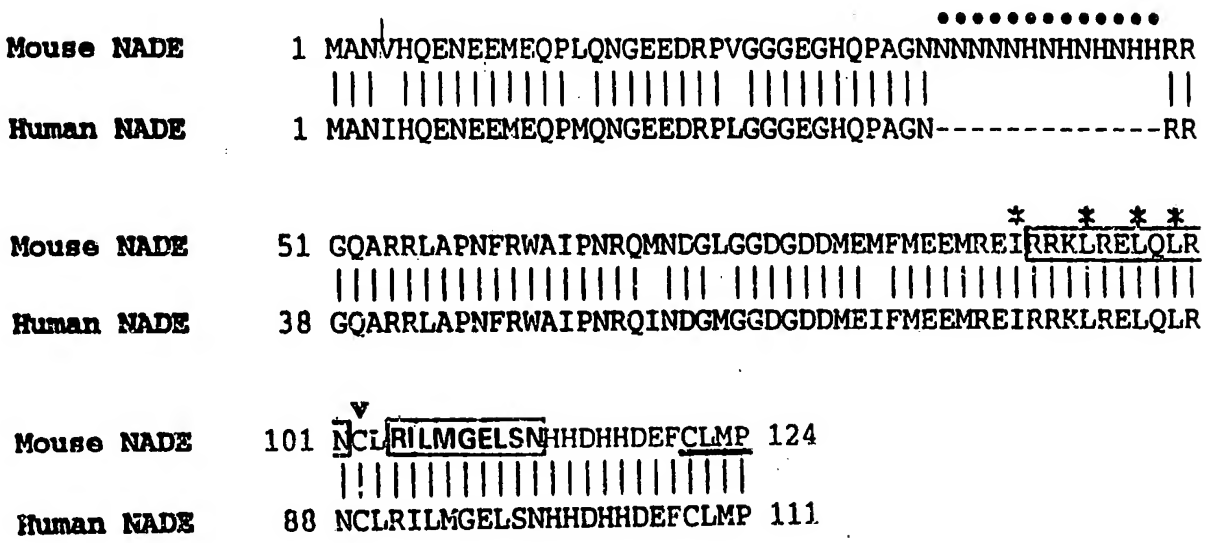


Figure 1A

cZyxin	319-331		L	T	M	K	E	V	E	E	L	E	L	L	T
MAPKK	32- 44		A	L	Q	K	K	L	E	E	L	E	L	D	E
PKI-α	37- 46			L	A	L	K	L	A	G	L	D	I		
TFⅢA	330-338				L	P	V	L	E	N	L	T	L		
RevHIV-1	73- 81				L	P	P	L	E	R	L	T	L		
RanBP1	178-189		K	V	A	E	K	L	E	A	L	S	V	R	
FMRP	425-437	E	V	D	Q	L	R	L	E	R	L	Q	I	D	
Gle1	351-356					L	P	L	G	K	L	T	L		
RexHTLV-1	81- 94	A	L	S	A	Q	L	Y	S	S	L	S	L	D	S
human NADE	65- 77	R	E	I	R	R	K	L	R	E	L	Q	L	R	
mouse NADE	88-100	R	E	I	R	R	K	L	R	E	L	Q	L	R	

Figure 1B

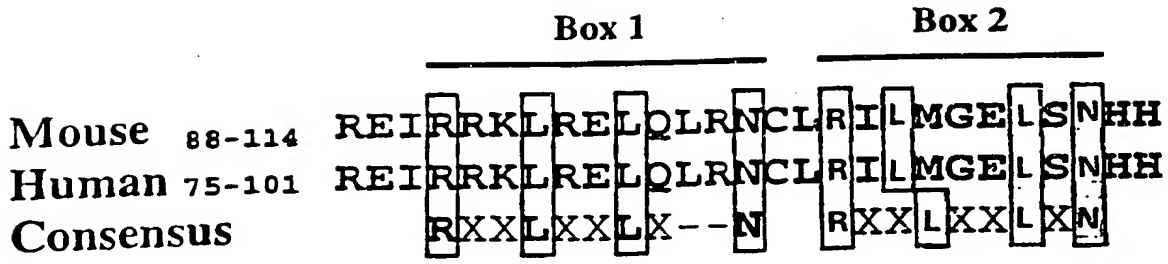

Box 1
Box 2
Mouse 88-114 REIRRKLRELQLRNCLRILMGELSNHH
Human 75-101 REIRRKLRELQLRNCLRILMGELSNHH
Consensus RXXLXXLX--N RXXLXXLXN

Figure 1C

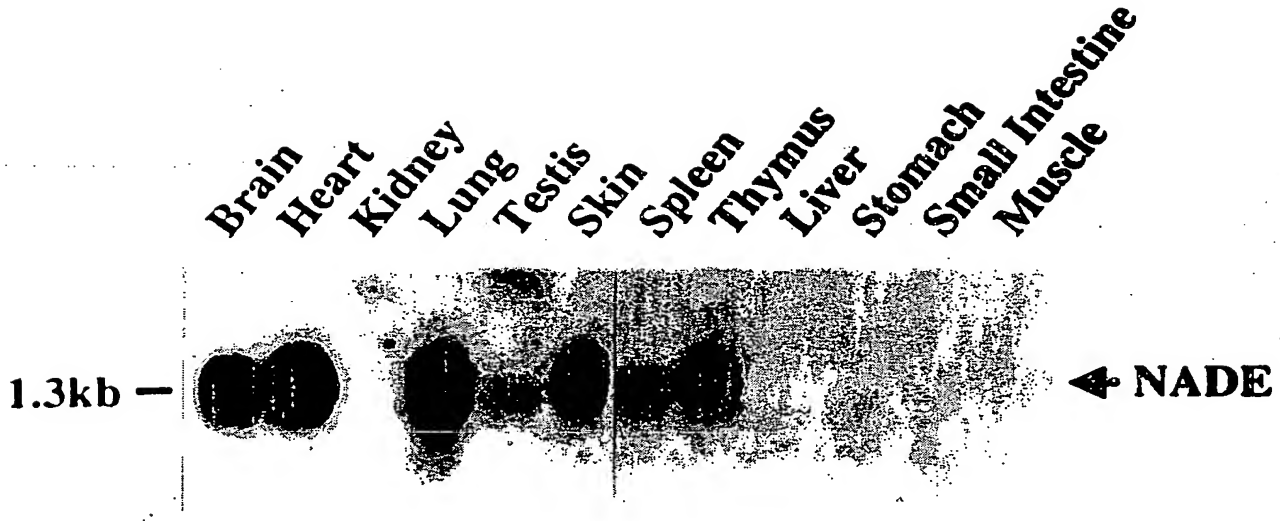
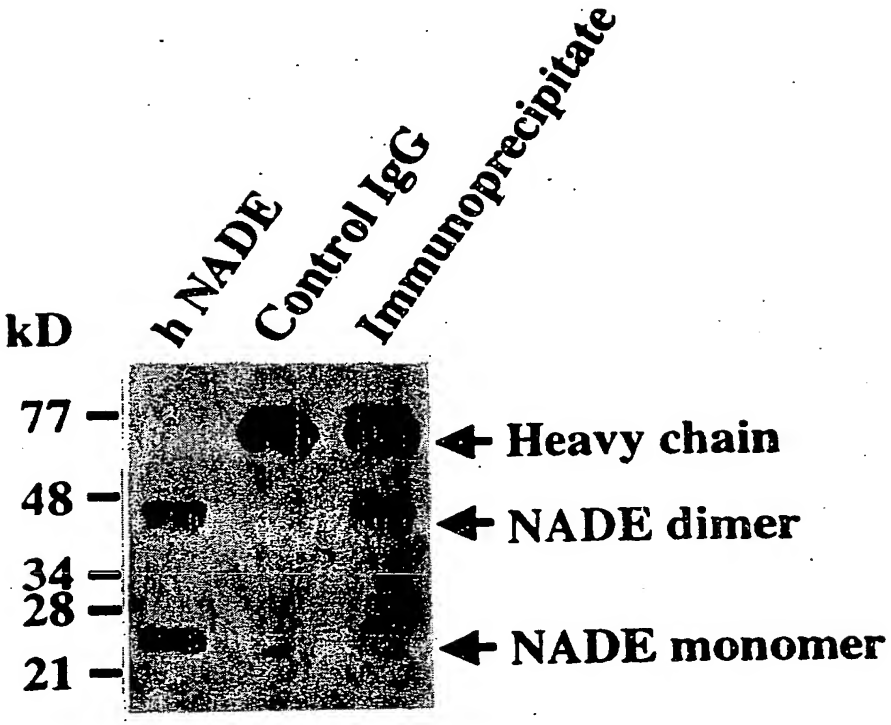

Brain
Heart
Kidney
Lung
Testis
Skin
Spleen
Thymus
Liver
Stomach
Small Intestine
Muscle
1.3kb
NADE

Figure 1D

Figure 1E


kD
h NADE
Control IgG
Immunoprecipitate
77
48
34
28
21
Heavy chain
NADE dimer
NADE monomer

5/29/1

Figure 1F

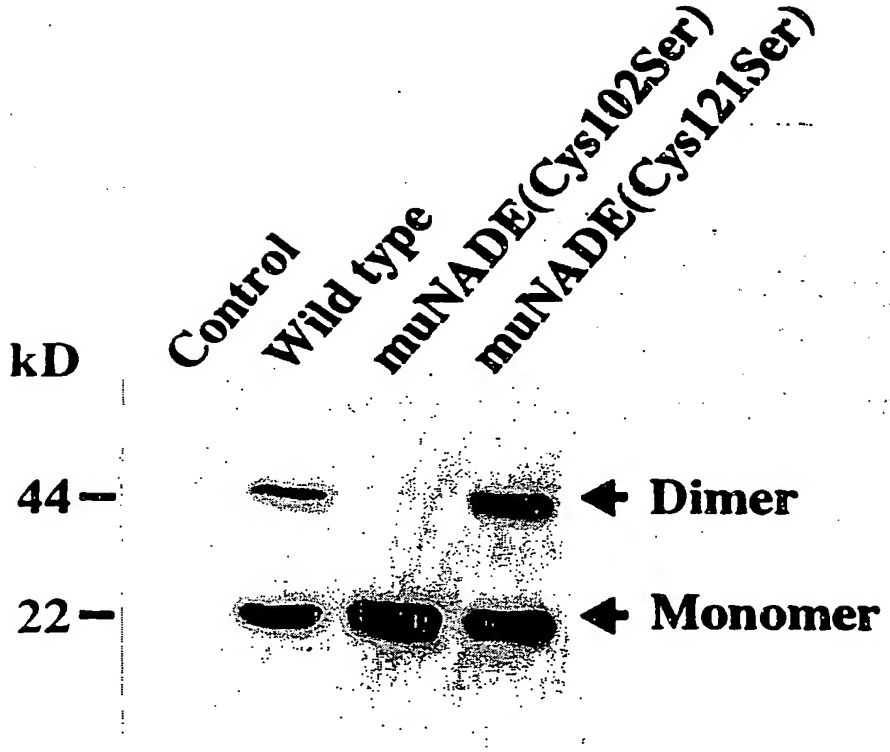


Figure 1G-1

Mouse

```
   1 acgagcgtctggccagcagctcggagctcctctgcgcgcggcgggctggcagcgggcccg  60
  61 aggcgagcgggacagattgactggaagccgagagtccaggcggcagcgggaattgacagg 120
 121 aggactacgccgcaagggataggcccagaatagcaaccaggaaacaaaatctcatcatgc 180
 181 ccaatgtccaccaggaaaacgaagagctggagcagcccctgcagaatggacaggaagacc 240
 241 gccctgtgggaggaggtgagggccaccagcctgctgcaaacaacaacaacaacaaccaca 300
 301 accataaccacaaccaccaccgaagaggccaggctcgccgacttgcccctaacttccgat 360
 361 gggccattcccaacaggcagatgaatgacgggttgggtggagatggagatgatatggaaa 420
 421 tgttcatggaggagatgagagagatccggagaaagcttagggagctacagctgagaaatt 480
 481 gtctacgcatccttatgggggagctgtctaaccaccacgatcaccatgatgaattctgcc 540
 541 ttatgccttgacttcggtcattcccccctgagatccatactgtgactcccgctgtagccc 600
 601 ttttcctcgcattttcctgacatgccctttaatgacccgtttgtggtgagcccttgtgttat 660
 661 ttccatgccatgtgccaggtggggcttgtgttgccagtga
```

Human

```
   1 accccatcccccactcctataccggtcctccattttggtgcctgcaaagctctgggaaaag  60
  60 aatcccgggaaacgaaaaatggtgggtttgggggaagggaggtaaggggagaaagctgga 120
 121 gggaggggctttaattggaggccccgtagaggacgcgcggaacttctaaggtgggaaaaa 180
 181 acgaaattaaaaaatcctttgatatcagggctctgaatcctgctggtcagagcaccaagc 240
 241 attcagtctctctccttgccttttgtcttacttgtgttcaaagaaaaacaaccagaaaaaa 300
 301 aaaatctcatcatggcaaatattcaccaggaaaacgaagagatggagcagcctatgcaga 360
 361 atggagaggaagaccgccctttgggaggaggtgaaggccaccagcctgcaggaaatcgac 420
 421 ggggacaggctcgccgacttgcccctaattttcgatgggccatacccaataggcagatca 480
 481 atgatgggatgggtggagatggagatgatatggaaatattcatggaggagatgagagaaa 540
 541 ttagaagaaaacttagggagctgcagttgaggaattgtctgcgtatccttatgggggagc 600
 601 tctctaatcaccatgaccatcatgatgaattttgccttatgccttgactcctgccatttt 660
 661 tcatgagattaatactgtgattcccgctgttttctttttccttgcattttcctaatatgc 720
 721 ctttactgatccgtttgctgtgaaccctatgttatttccatgtgtcaagtgggtcttgtg 780
 781 ttgccagcttctatttgaagattgccttgcactcagtgtaagtttctgtcagcagtagt 840
 841 ttcacccatttgcatggaaaaatttaaagctaataaagcaatttaaaaagc
```

Figure 1G-2

```
                1              15 16          30 31          45 46          60 61          75 76          90
 1 musnade3a MESKD-QGVKNLNME NDHQKKEEKEEKP-QDTIRREPAVALISEAG KNCAPR-----------GGRRRFRVR QPIAHYRWDLMQRVG EPQGRMREENVQRFG
 2 hunade3a1 MESKEERALNNLIVE NVNQENDEKDEKE-QVANKGEPL-ALPLNVS EYCVPR-----------GNRRRFRVR QPILQYRWDIMHRLG EPQARMREENMERIG
 3 hunade3a2 MESKEKRAVNSLSME NANQEN---EEKE-QVANKGEPL-ALPLDAG EYCVPR-----------GNRRRFPVR QPILQYRWDIMHRLG EPQARMREENMERIG
 4  ratnad3a MESKD-QGAKNLNME NDHQKKEEKEEKP-QDTIKREPVVAPTFEAG KNCAPR-----------GGRRRFRVR QPISHYRWDLMHRVG EPQGRMREENVQRFG
 5  ratnad3b MASKVKQVILDLTVE KDKKNKKGGKASK-QSEEES---HHLEEVEN KKP--------------GGNVRRKVR RLVPNFLWAIPNRHV D-----HSEGGEEVG
 6 musnade3b MASKFKQVILDLTVE KDKKDKRGGKASK-QSEEEP---HHLEEVEN KKP--------------GGNVRRKVR RLVPNFLWAIPNRHV D-----RNEGGEDVG
 7  humnade1              MA NIHQENEEMEQPM-QNGEEDRPLGGGEGHQPA -----------------GNRRGQAR RLAPNFRWAIPNRQI N---DGMGGDGDDME
 8  ratnade1                        MEQPL-QNGQEDRPVGGGEGHQPAAANNNHNHNHNHNHSHNHNHHRRGQAR RLAPNFRWAIPNRQM N---DGLGGDGDDME
 9  musnade1              MA NVHQENEEMEQPL-QNGQEDRPVGGGEGHQPAANNNNNNHNHNHNHH------RRGQAR RLAPNFRWAIPNRQM N---DGLGGDGDDME
10 humnade2              ME NVPKENKVVEKAPVQN--EAPALGGGEYQEP -----------------GGNVKGVWA PPAPGFGEDVPNRLV D-NIDMIDGDGDDME

Page 2.1
                91             105 106         120 121         135 136         150 151         165 166         180
 1 musnade3a GDVRQLME---KLRE RQLSHSLRAVSTDPP- HHDHHDEFCLMP    130
 2 hunade3a1 EEVRQLME---KLRE KQLSHSLRAVSTDPP -HHDHHDEFCLMP
 3 hunade3a2 EEVRQLME---KLRE KQLSHSLRAVSTDPP -HHDHHDEFCLMP    125
 4  ratnad3a EDMRQLME---KLRE RQLSHSLRAVSTDPP -HHDHHDEFCLMP
 5  ratnad3b RFVGQVMEAKRKSKE QQMRPYTRFRTPEPD NHYD----FCLIP
 6 musnade3b RFVVQGTEVKRKTTE QQVRPYRRFRTPEPD NHYD----FCLIP    97
 7  humnade1 IFMEEMREIRRKLRE LQLRNCLRILMGELS NHHDHHDEFCLMP
 8  ratnade1 MFMEEMREIRRKLRE LQLRNCLRILMGELS NHHDHHDEFCLMP
 9  musnade1 MFMEEMREIRRKLRE LQLRNCLRILMGELS NHHDHHDEFCLMP
10 humnade2 RFMEEMRELRRKIRE LQLRYSLRILIGDPP -HHDHHDEFCLMP
```

Figure 1H

Figure 2A

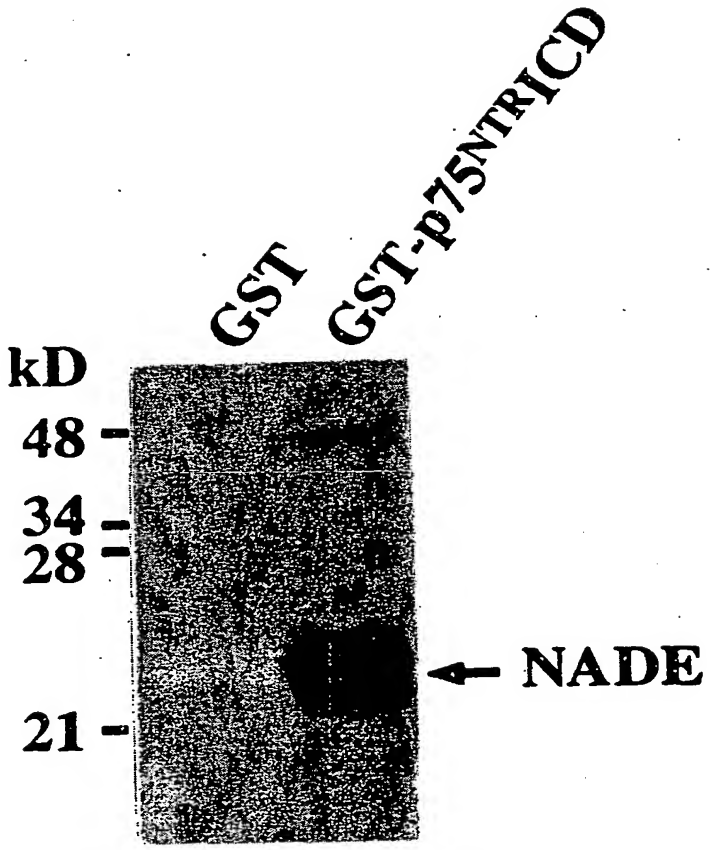
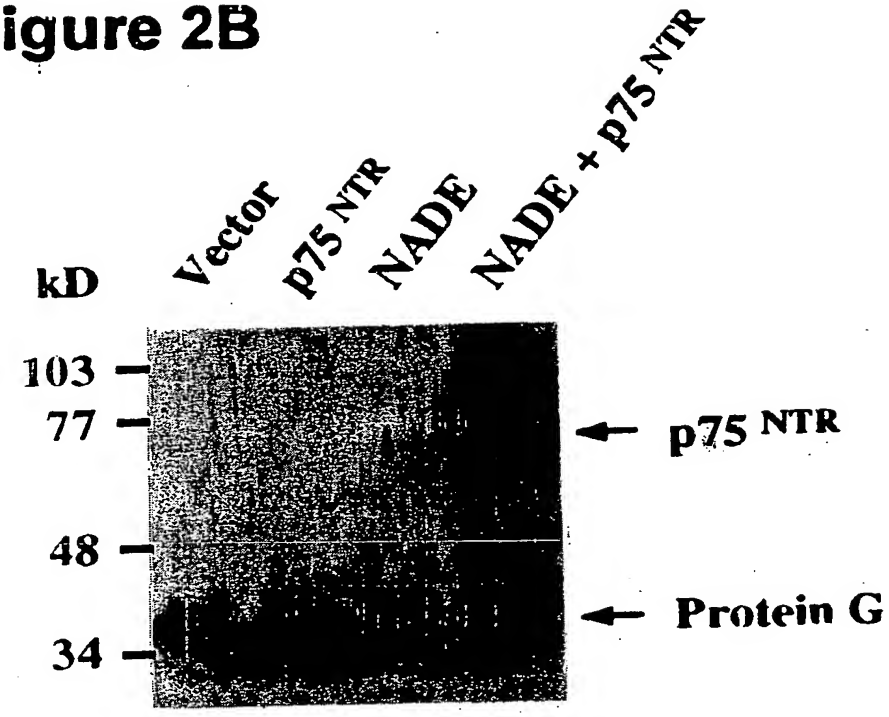


Figure 2B


Vector
p75 NTR
NADE
NADE + p75 NTR
kD
103
77
48
34
p75 NTR
Protein G

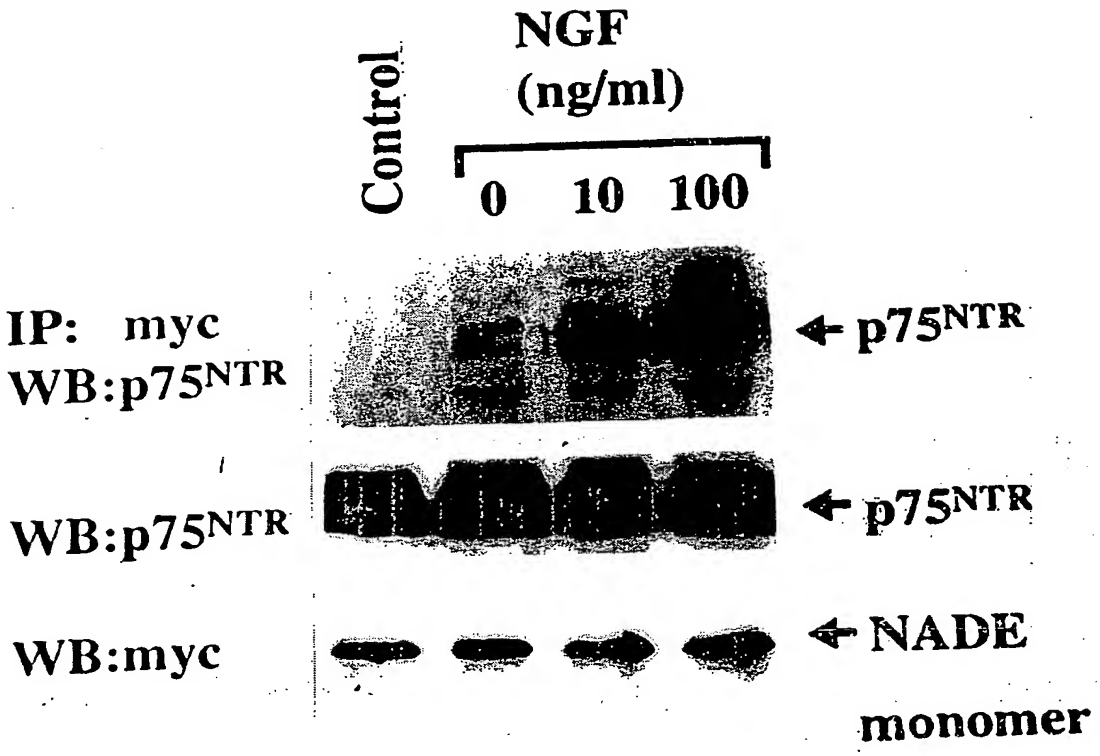

Control
NGF
(ng/ml)
0
10
100
IP: myc
WB:p75NTR
p75NTR
WB:p75NTR
p75NTR
WB:myc
NADE
monomer

Figure 2C

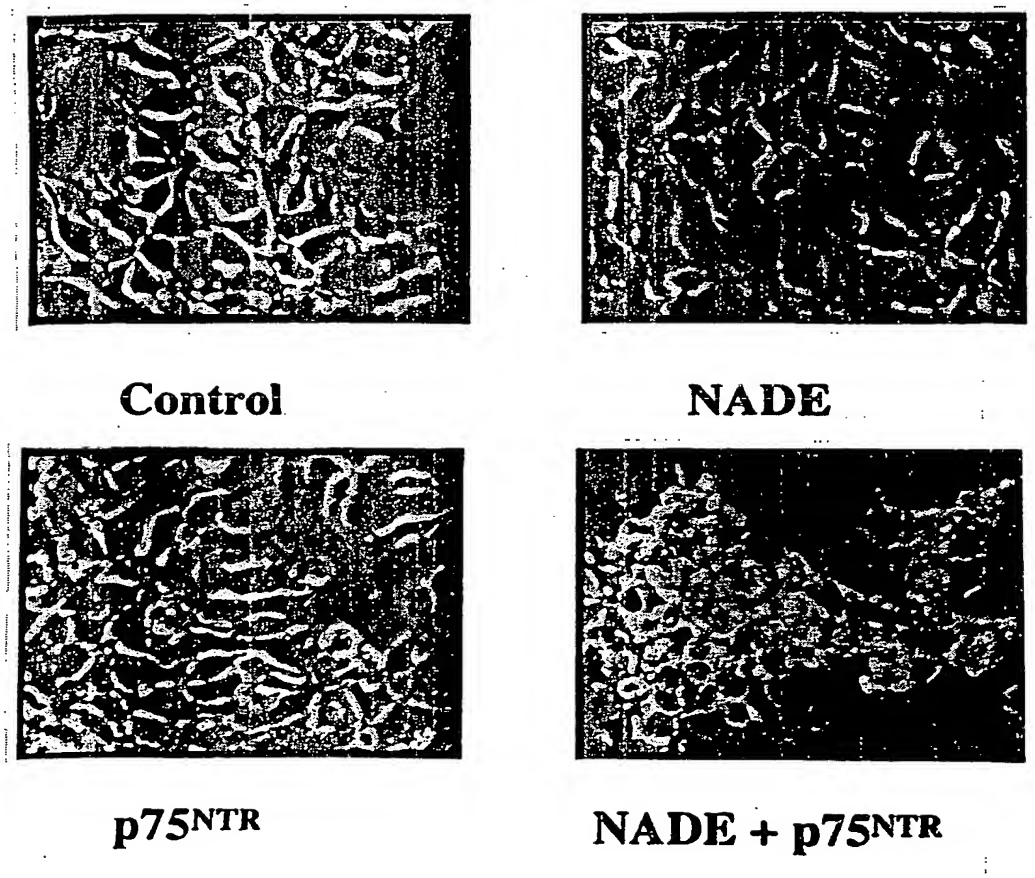
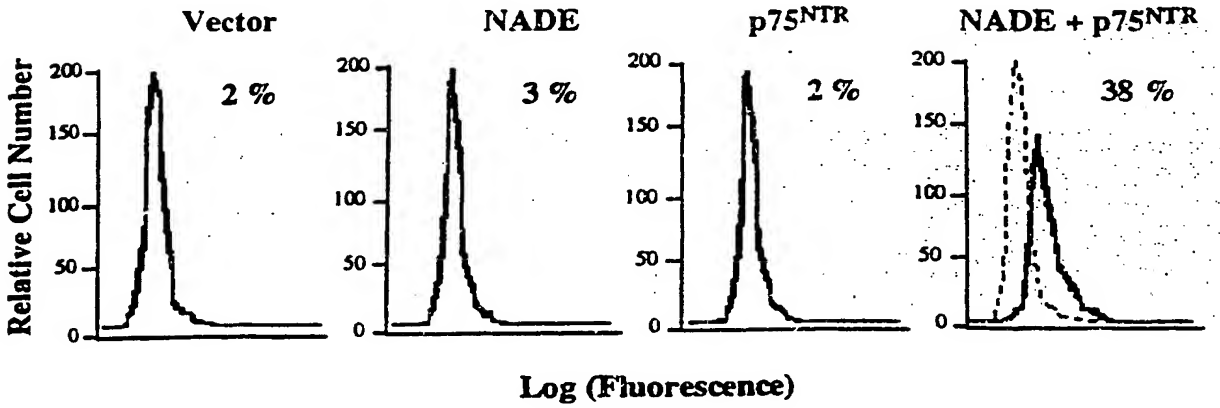


Figure 3A

Figure 3B-1 Figure 3B-2 Figure 3B-3 Figure 3B-4



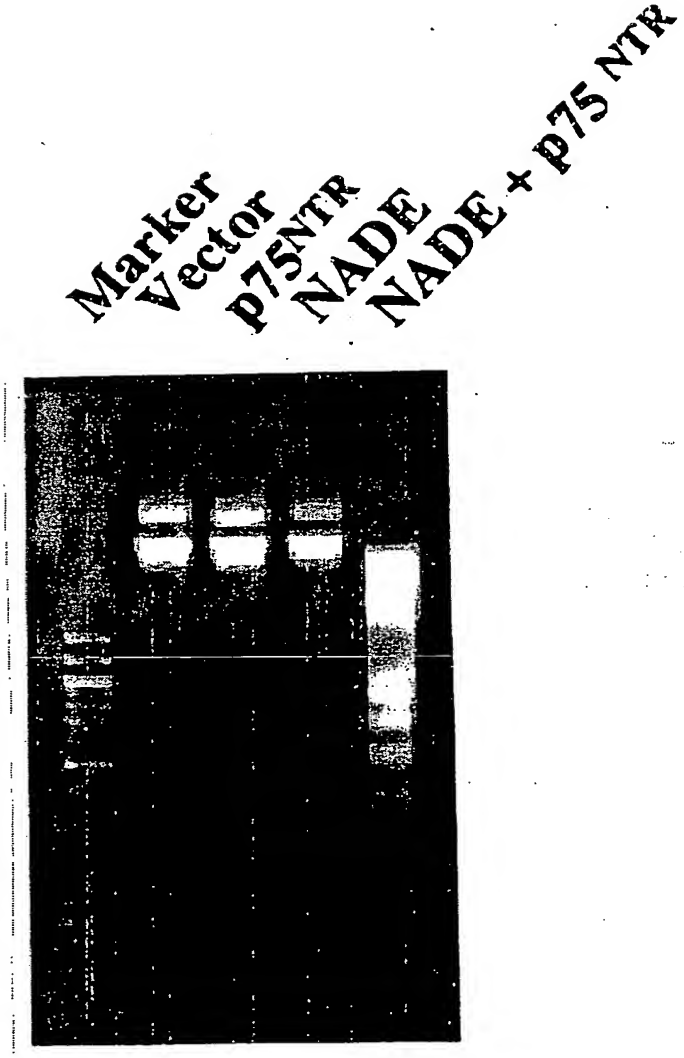


Figure 3C

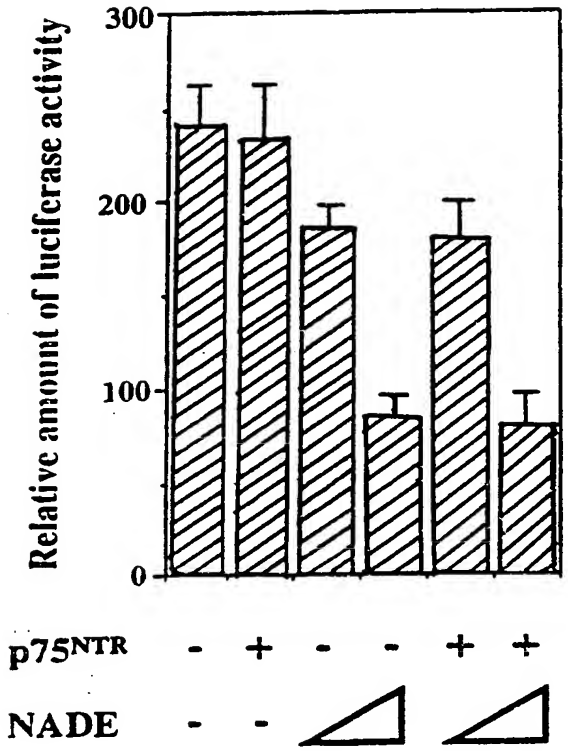

Relative amount of luciferase activity
300
200
100
0
p75NTR - + - - + +
NADE - -

Figure 3D

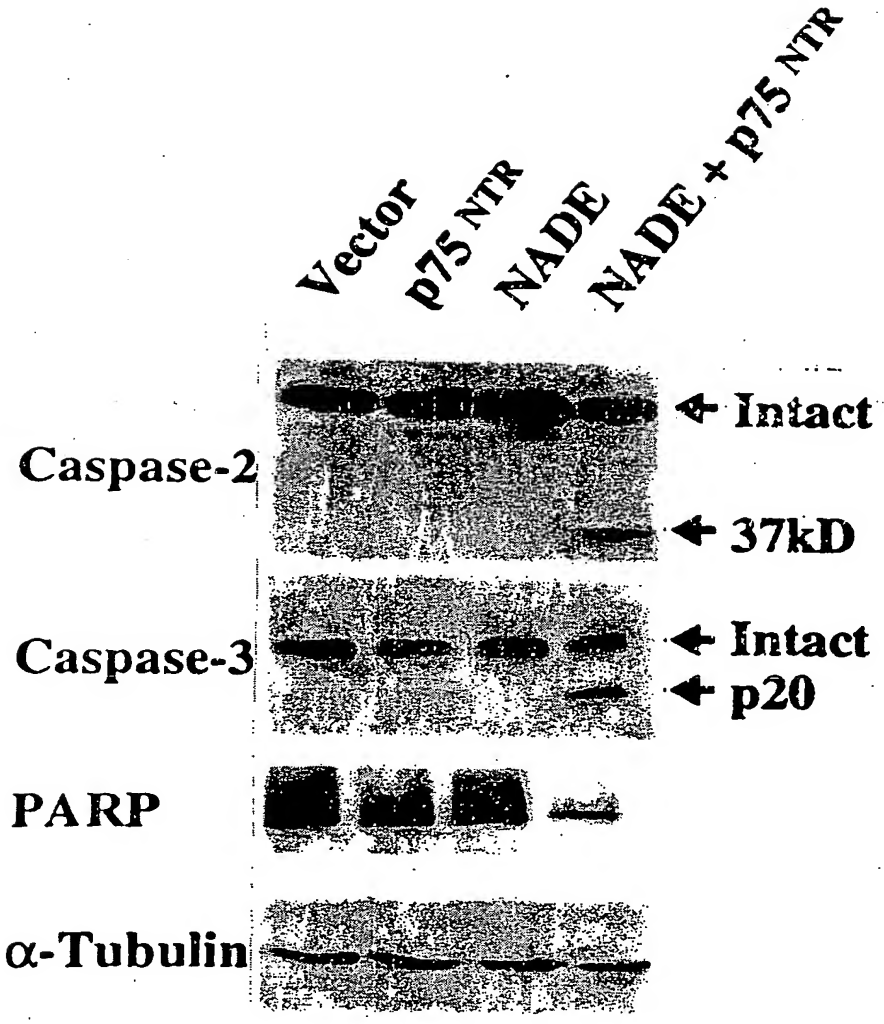
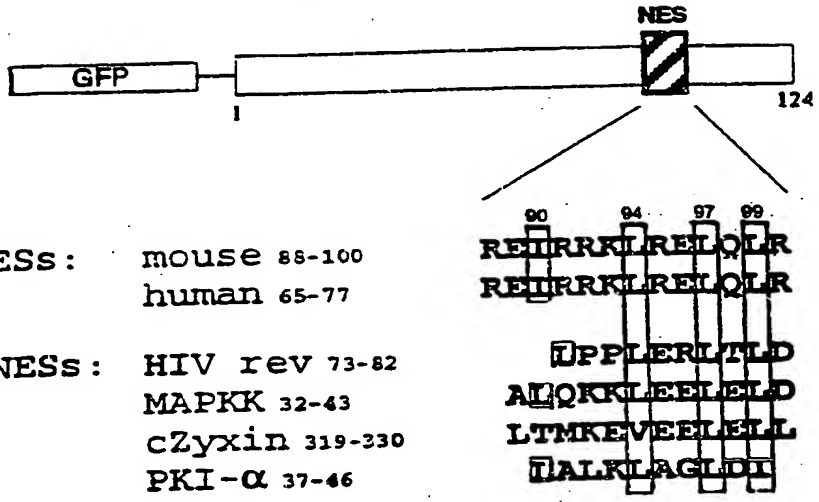

Vector
p75 NTR
NADE
NADE + p75 NTR
Caspase-2
Intact
37kD
Caspase-3
Intact
p20
PARP
α-Tubulin

Figure 3E

Figure 4A

WT mouse NADE-GFP



NADE NESs: mouse 88-100
human 65-77

Other NESs: HIV rev 73-82
MAPKK 32-43
cZyxin 319-330
PKI-α 37-46

Figure 4B

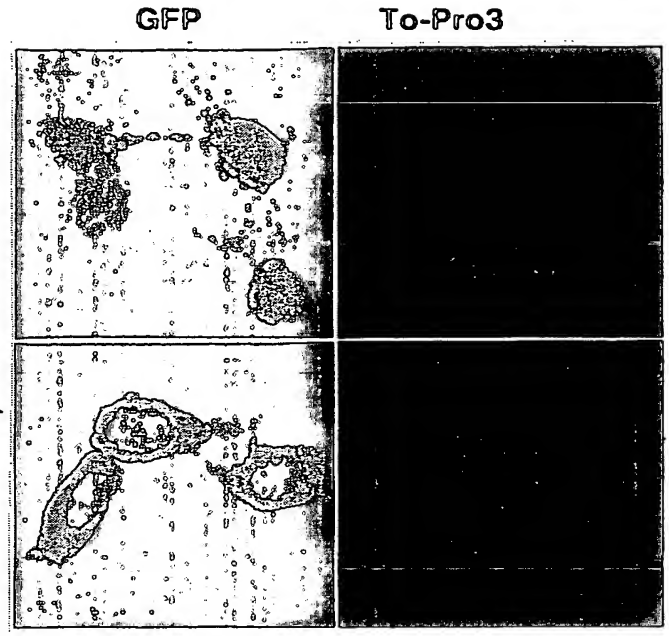


Figure 4C

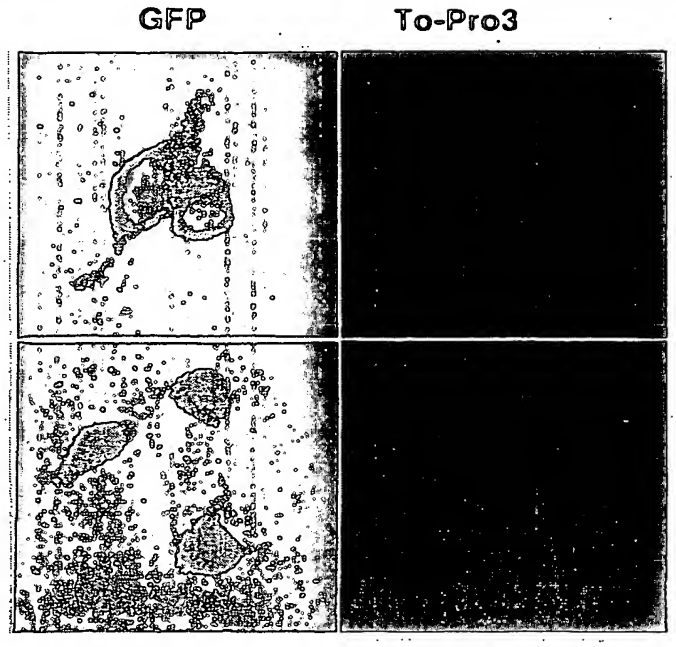


Figure 4D

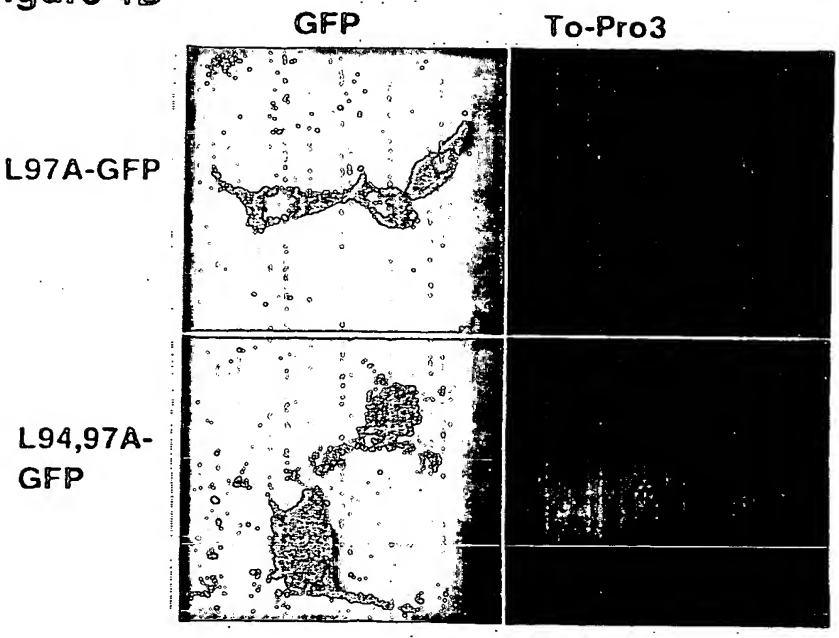


FIGURE 5A

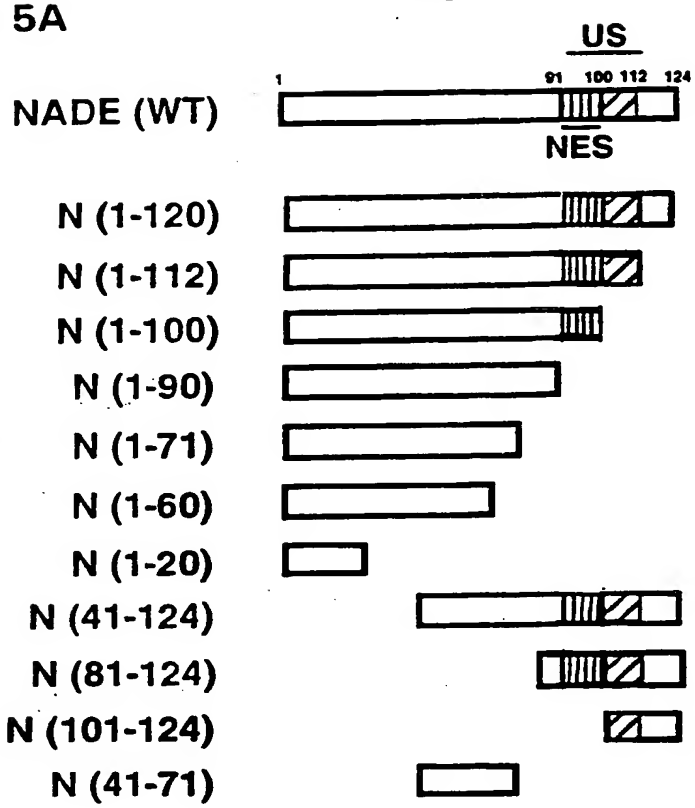
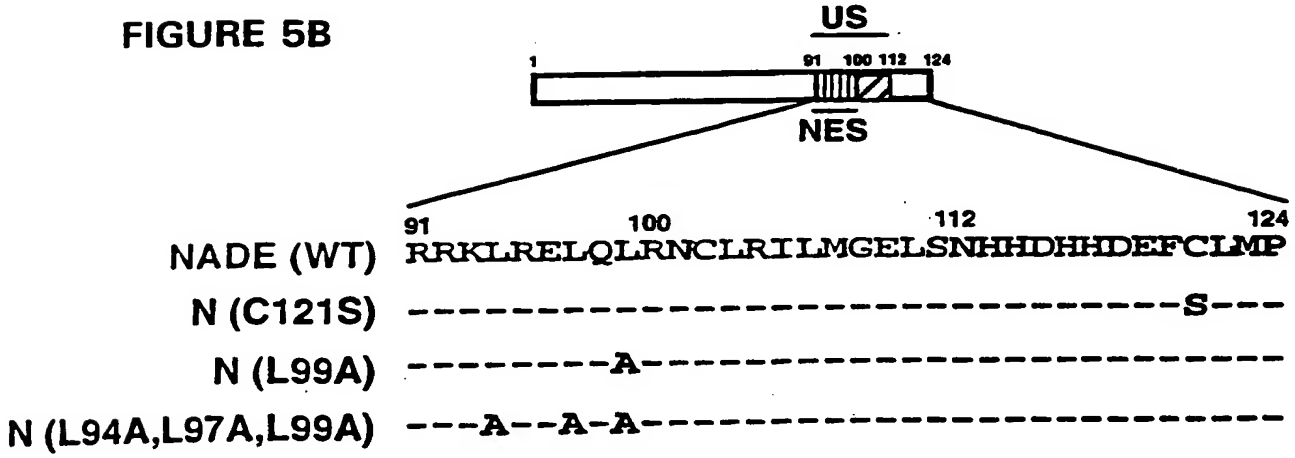


FIGURE 5B



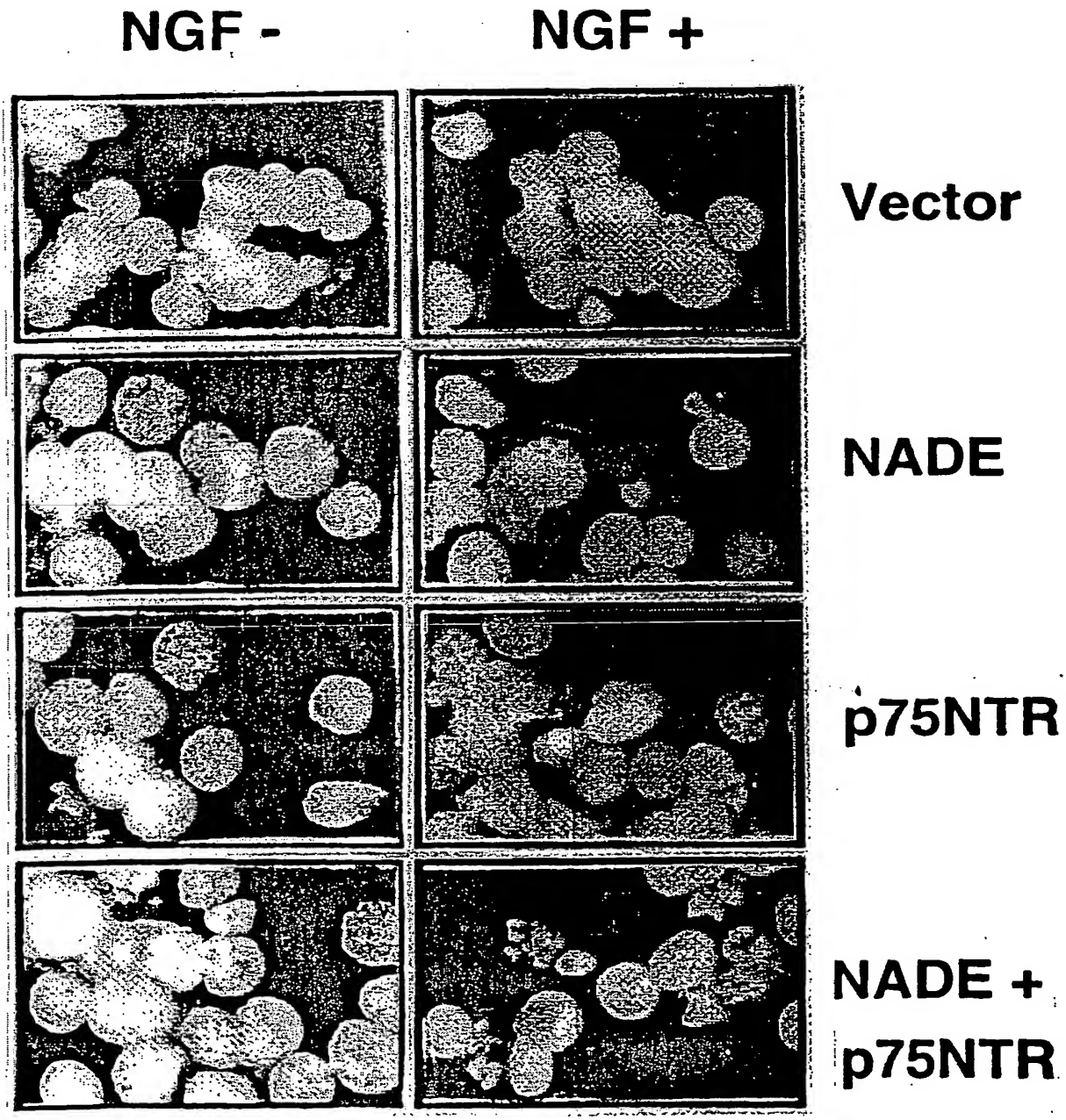


FIGURE 6A

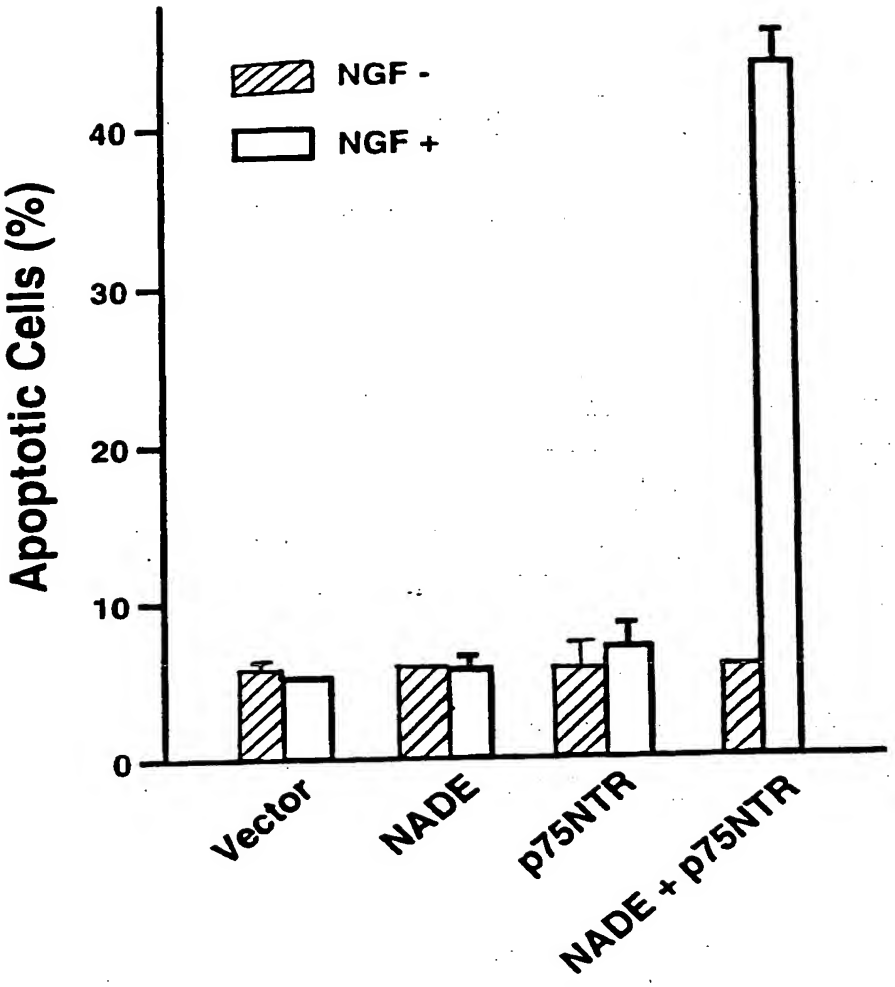

NGF -
NGF +
Apoptotic Cells (%)
0
10
20
30
40
Vector
NADE
p75NTR
NADE + p75NTR

FIGURE 6B

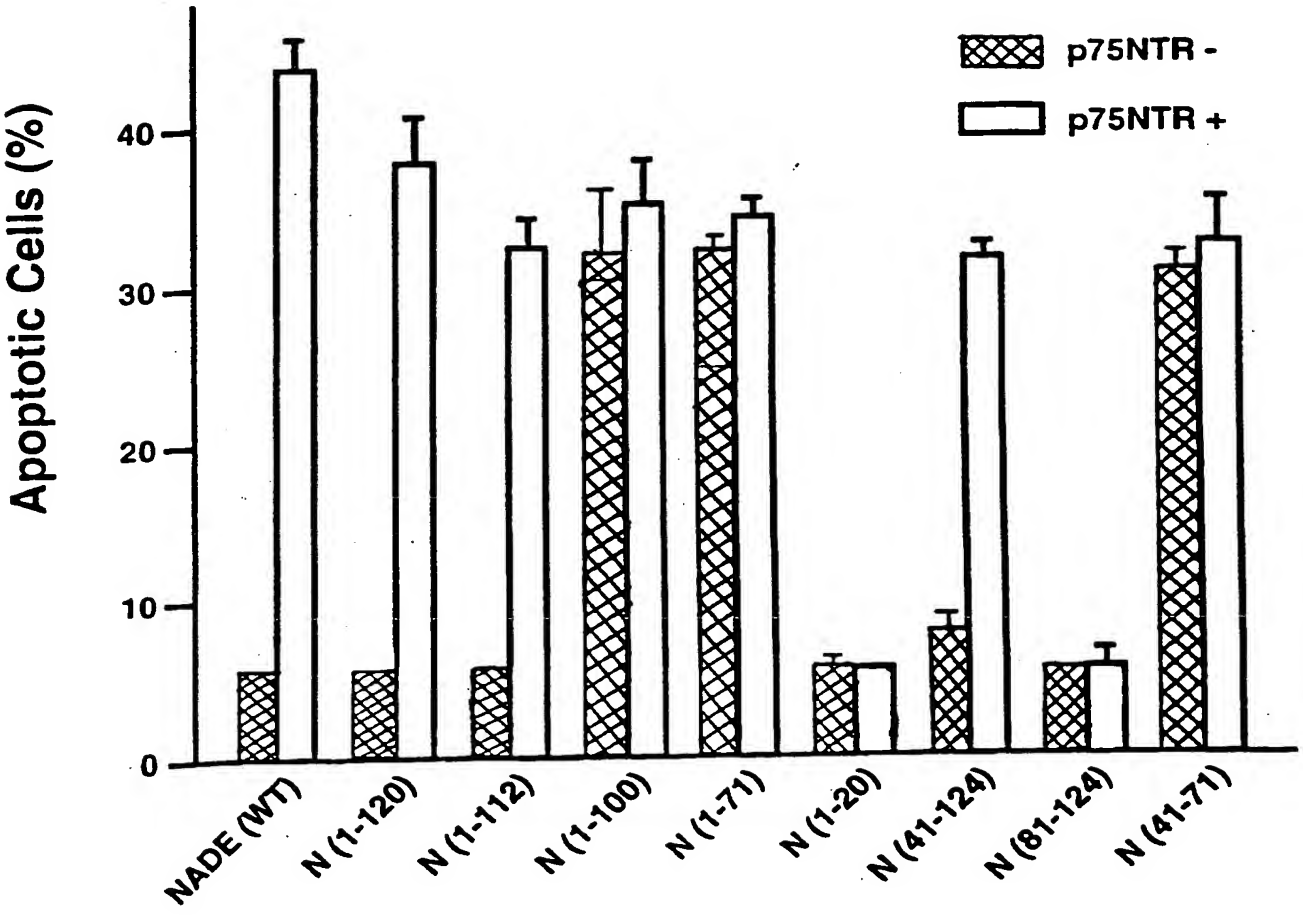

p75NTR -
p75NTR +
Apoptotic Cells (%)
0
10
20
30
40
NADE (WT)
N (1-120)
N (1-112)
N (1-100)
N (1-71)
N (1-20)
N (41-124)
N (81-124)
N (41-71)

FIGURE 7

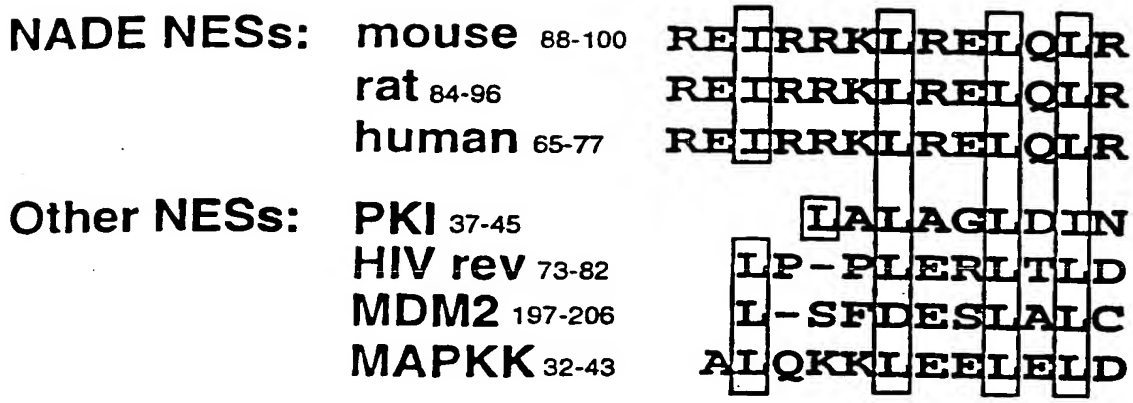
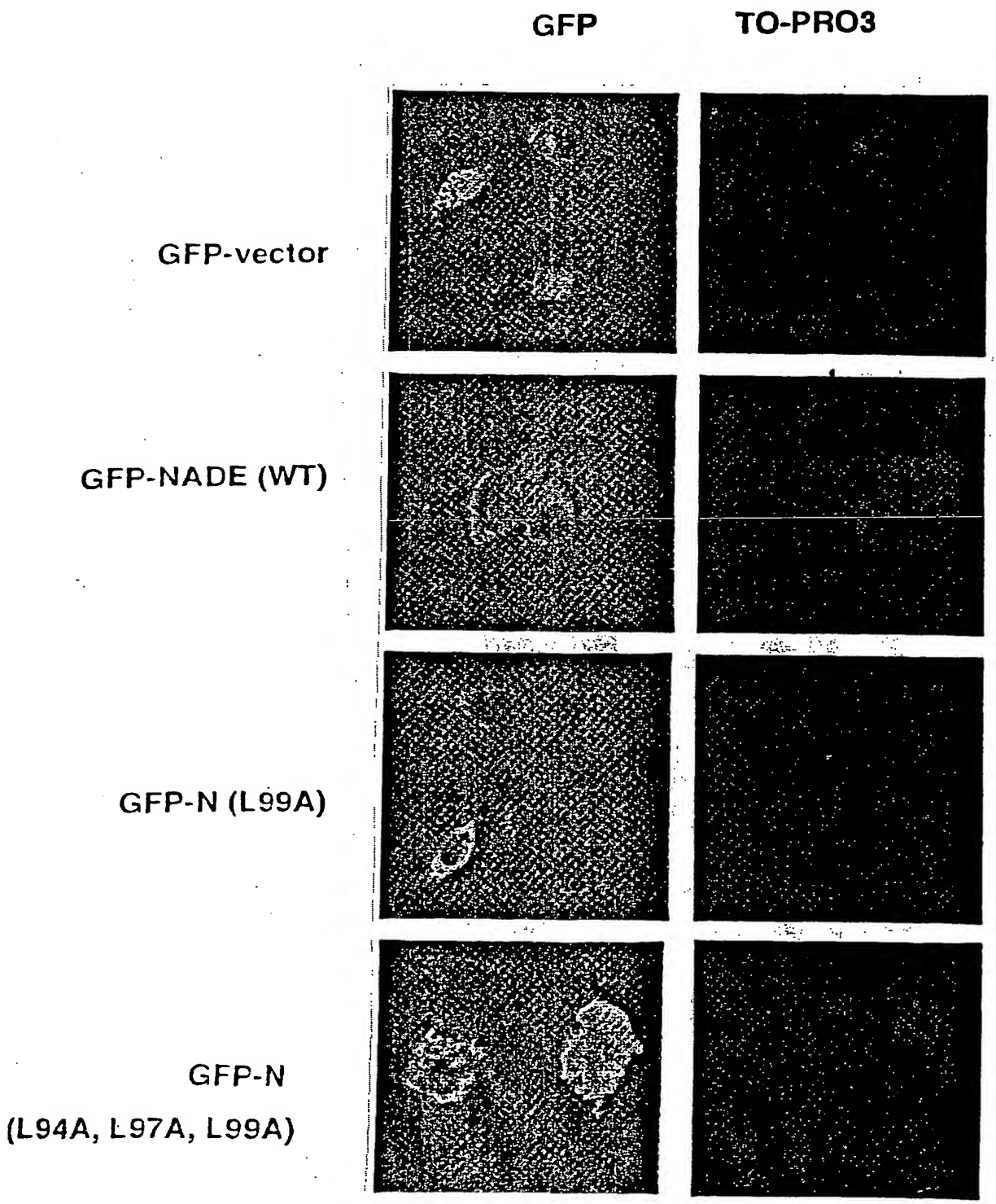

NADE NESs:
mouse 88-100
rat 84-96
human 65-77
Other NESs:
PKI 37-45
HIV rev 73-82
MDM2 197-206
MAPKK 32-43
RELRRKLRELQLR
RELRRKLRELQLR
RELRRKLRELQLR
LALAGLDIN
LP-PLERLTLD
L-SFDESLALC
ALQKKLEELELD

FIGURE 8A

Figure 8B


GFP
TO-PRO3
GFP-vector
GFP-NADE (WT)
GFP-N (L99A)
GFP-N
(L94A, L97A, L99A)

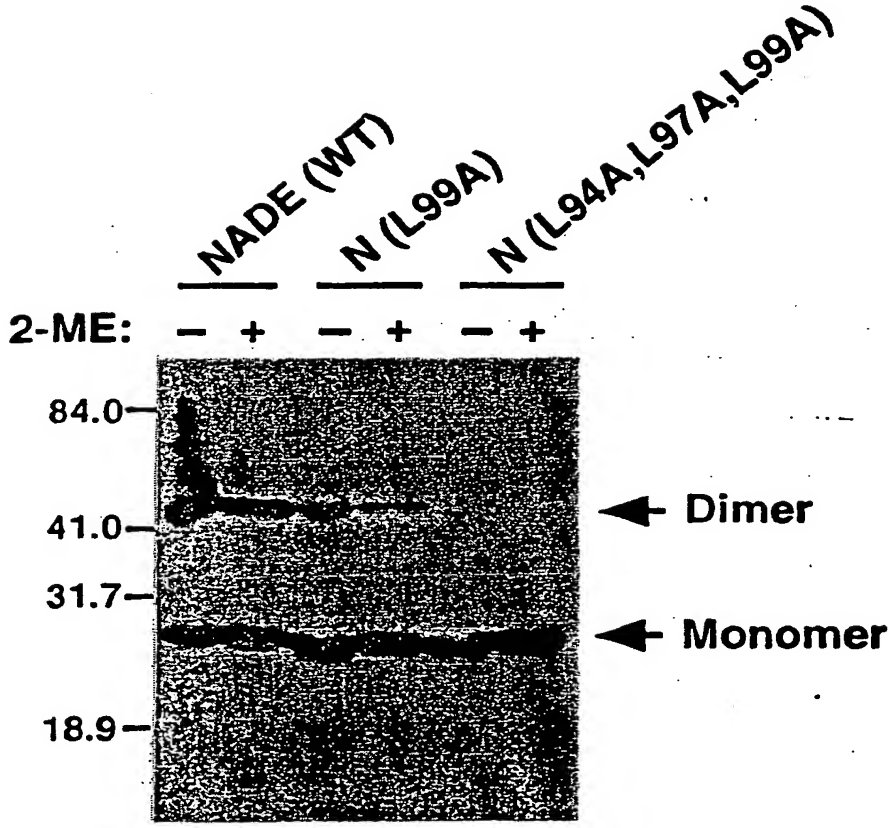

NADE (WT)
N (L99A)
N (L94A,L97A,L99A)
2-ME: – + – + – +
84.0
41.0
31.7
18.9
Dimer
Monomer

FIGURE 8C

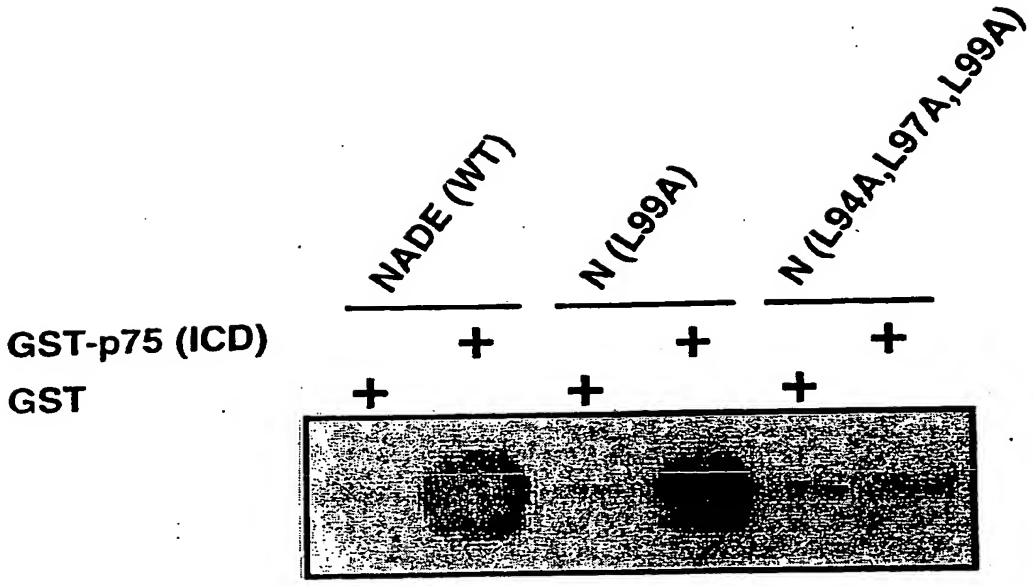


FIGURE 8D

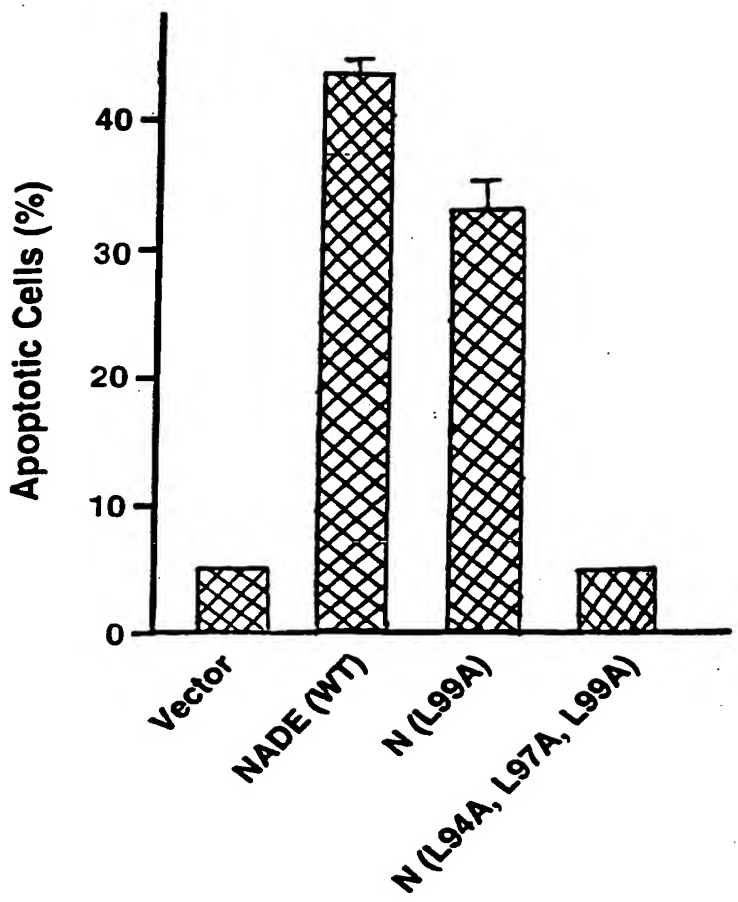

Apoptotic Cells (%)
40
30
20
10
0
Vector
NADE (WT)
N (L99A)
N (L94A, L97A, L99A)

FIGURE 8E

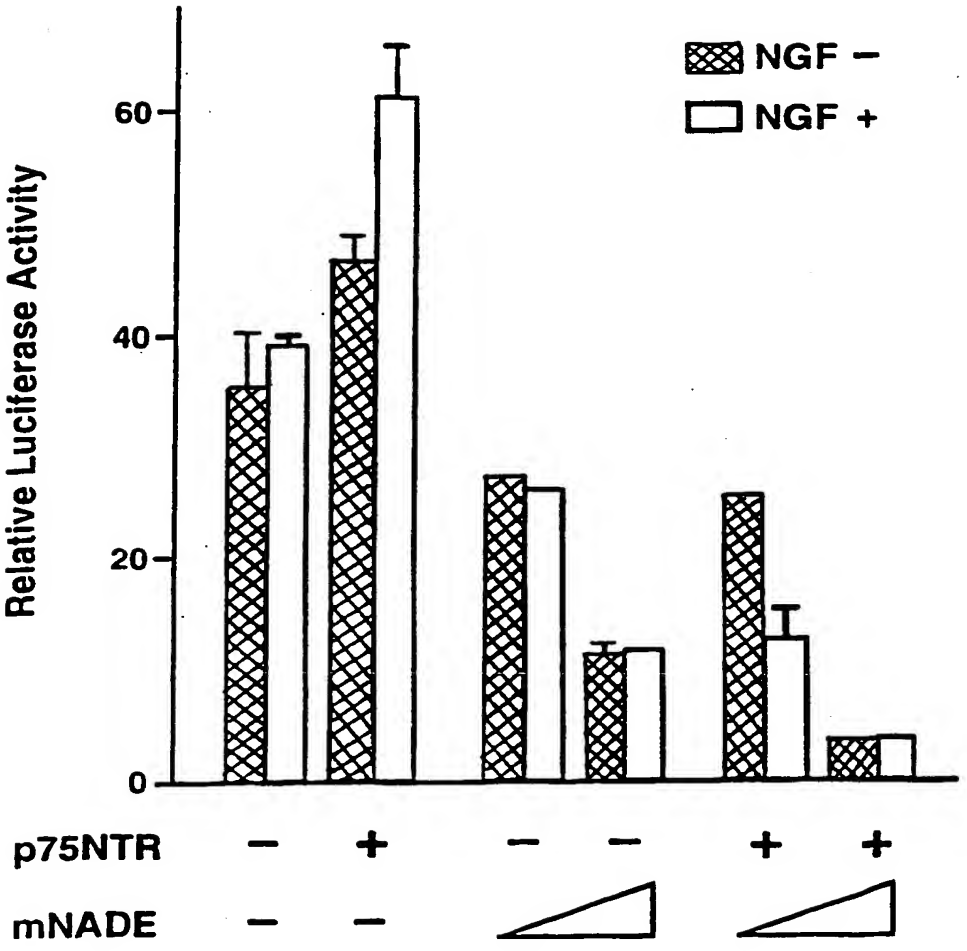

NGF −
NGF +
Relative Luciferase Activity
60
40
20
0
p75NTR − + − − + +
mNADE − −

FIGURE 9A

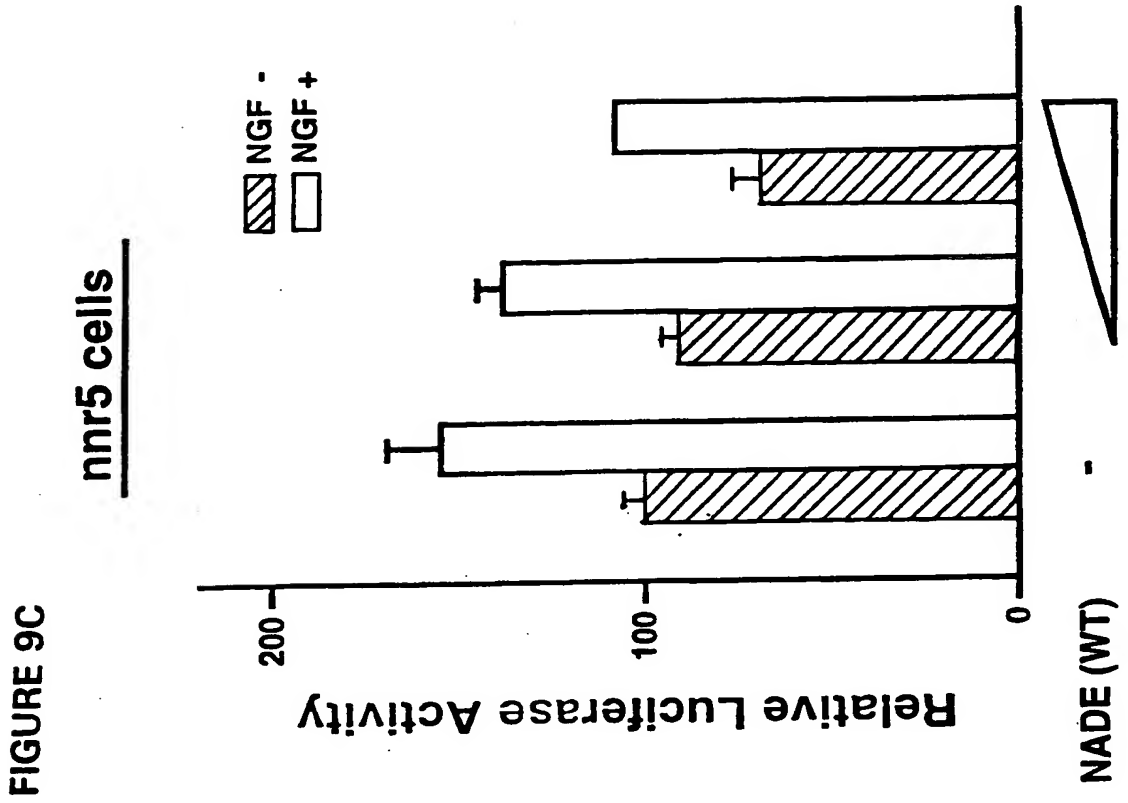


FIGURE 9C

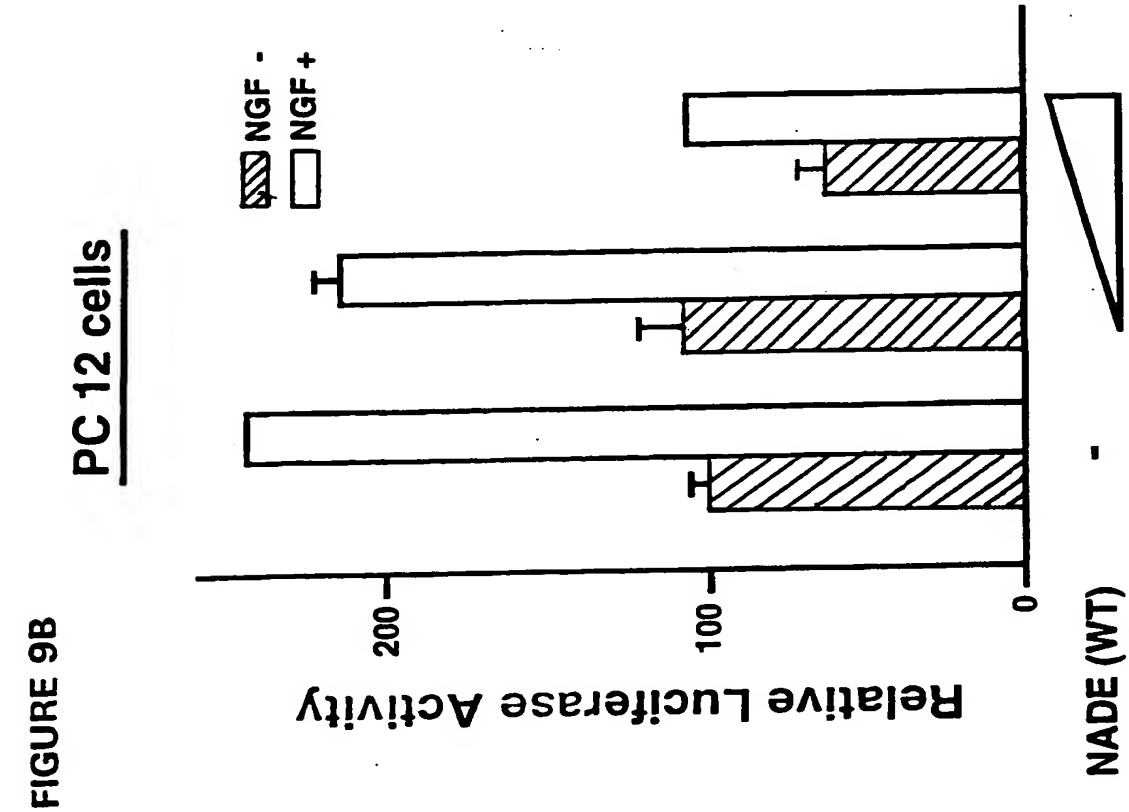


FIGURE 9B

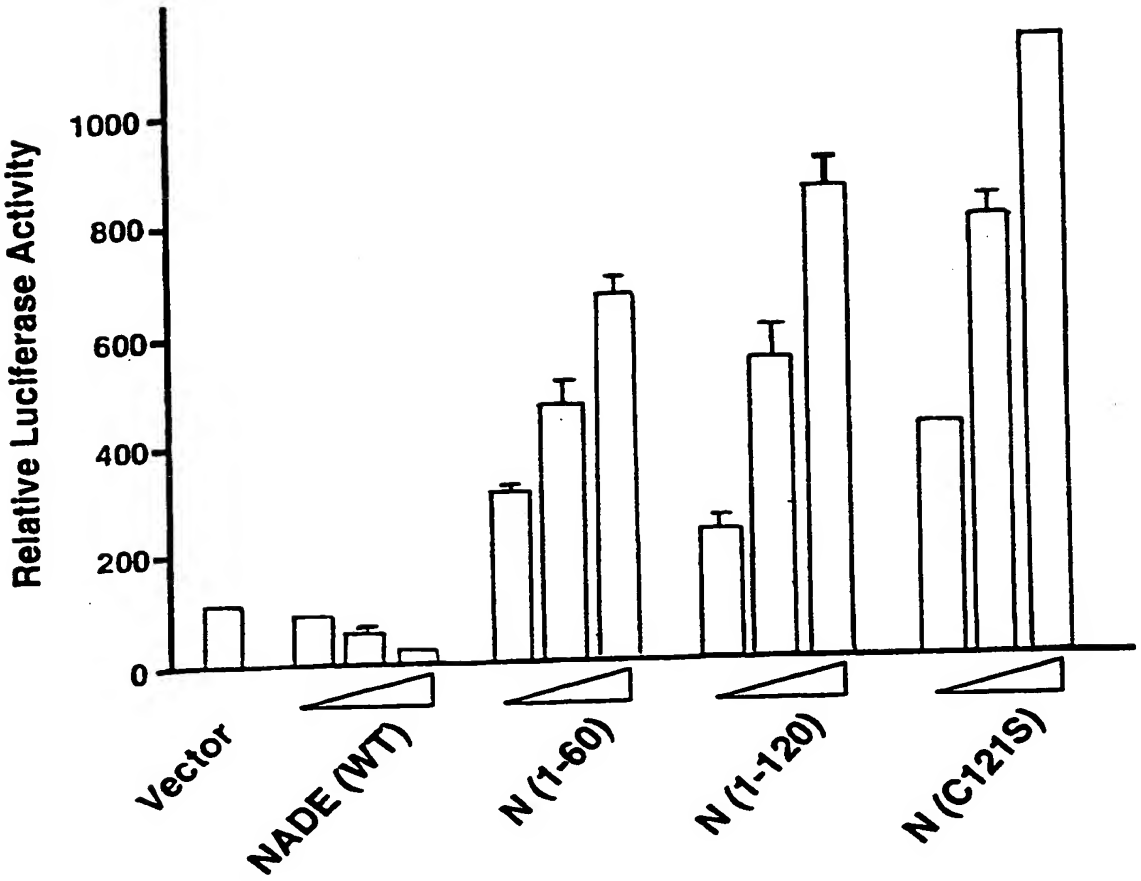

Relative Luciferase Activity
1000
800
600
400
200
0
Vector
NADE (WT)
N (1-60)
N (1-120)
N (C121S)

FIGURE 10

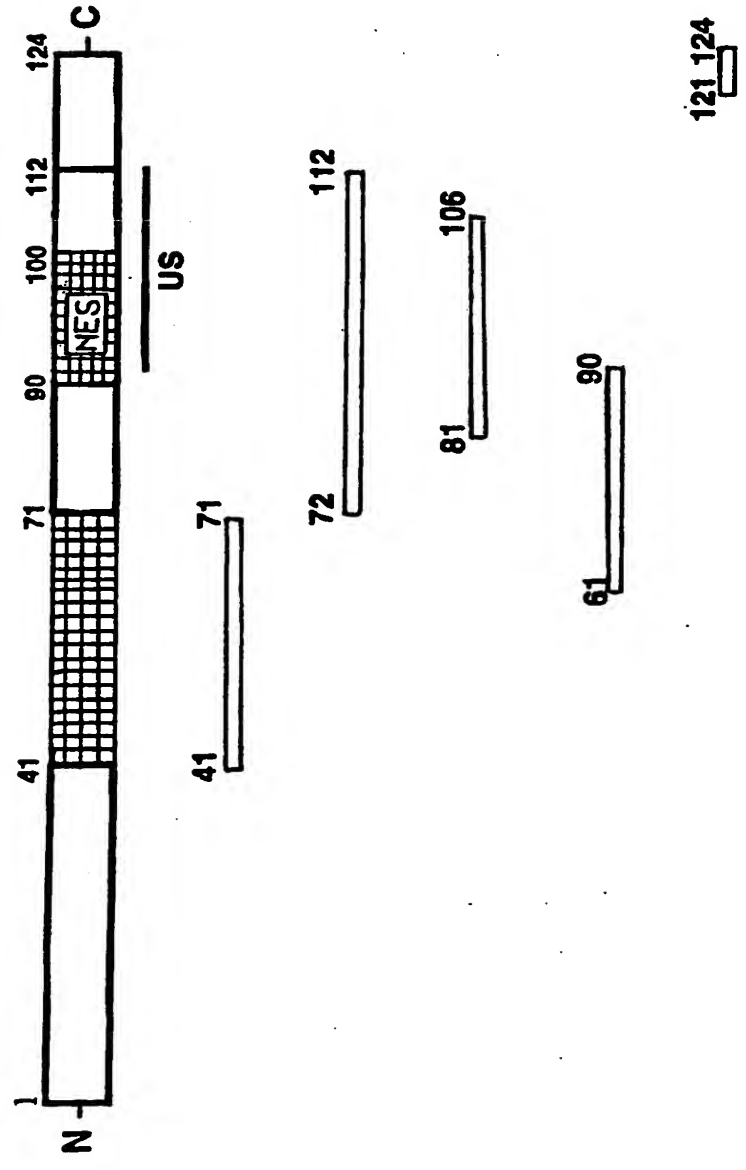

NADE (WT)
Pro-apoptotic domain
Regulatory domain
p75NTR-binding domain
NF-κB suppression domain
NF-κB suppression domain
C
N
124
112
100
90
71
41
1
NES
US
71
41
112
72
106
81
90
61
121 124

FIGURE 11